



# **Vaccine Healthcare Centers (VHC) Network**

## **Update on Rare Adverse Events**

### **Armed Forces Epidemiological Board**

### **11 May 2004 (1315-1330)**

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# **VHC Network**

## **Update on the Network**

- Official opening of Naval Medical Center Portsmouth (NMCP): 26 April 2004
- Other sites operational with opening ceremony pending:
  - Womack AMC, Fort Bragg, NC
  - Wilford Hall MC, San Antonio, Texas
- Funding for Network with 4 regional sites supporting DoD worldwide
  - FY04: no unfunded requirement
  - FY05: unfunded requirement
  - Submission for FY06 POM completed



# VHC Network

## Update on the Network

- Request for consultative support continue
  - Staff at each of sites collaborative in virtual Network to support mission requirements
- > 1000 cases reviewed by VHC Network since 2001 opening of 1<sup>st</sup> regional site
- Emergent response in 2003 to support in depth VAERS reviews for myopericarditis
  - 71 cases meet CDC/DoD case definitions
  - 6 additional under review
  - 23 cases did not meet CDC/DoD case definitions but are being followed for outcomes



# Oropharyngeal Shedding of Vaccinia Post Immunization

Questions/concerns regarding risk of vaccinia transmission through oropharyngeal shedding

- Jan 2003: started protocol to determine if viral shedding could be detected in the oropharynx
  - Viral culture by gold standard method
  - Specific antigen by electrochemiluminescence
  - Specific DNA by PCR
- 144 subjects studied with 89 completing all post vaccination swabs (0,1-3,4-6,7-9,10-12,13-15 days)
  - All studies negative = 95% CI of less than 3.3% chance of any evidence of vaccinia shedding in the oropharynx
- Data supports ACIP guidelines and reassures those with continued concerns about risk of respiratory transmission



# Vaccinia Contact Transmission

- VHC Network provided in-depth VAERS reports – Support for review of risk factors and outcomes
- Presentation at National Immunization Conference: **Vaccinia Contact Transfer: The US Military Smallpox Vaccination Experience**
  - MT Huynh\*, MD, MPH; LL Duran, APRN; LC Collins, Jr., MD; D Bradshaw, MD, MPH; J Grabenstein, RPh, Ph.D.
- Risk factors for contact vaccinia: 29 cases
  - Intimate and/or close or personal skin-to-skin contacts: e.g., wrestling
  - No unexplained transmission events



# **Myopericarditis Post Vaccinia Immunization**

- VHC Network staff supported VAERS case review process critical to the data review that follows this presentation
  - Dr. Eckart – update on follow up VAERS information on cases meeting CDC/DoD case definitions
  - Dr. Atwood – DoD dilated cardiomyopathy cases update
- Prospective myopericarditis protocol fully approved at WRAMC and BAMC



# Myopericarditis Post Vaccinia & Influenza Vaccination

- Prospective protocol: WRAMC & Brooke AMC approved
  - **600 primary vaccinia recipients - pending modification based on ACAMBIS study - include vaccinees receiving other vaccines**
  - 200 influenza vaccinees
  - Hypothesis: 2-3% incidence of subclinical myopericarditis
- Assess incidence of clinical & subclinical myopericarditis: monitor pre and post
  - ECGs, enzymes, inflammatory markers
  - Case identification: run case controlled study for more detailed immunologic assays & immunogenetics
- Initial funding through collaboration with CDC-Clinical Immunization Safety Assessment (CISA) Center Northern CA Kaiser/U of Washington Molecular Immunology Dep
- Companion protocol needed to standardize special cardiac studies on all patients, assess inflammation & outcomes

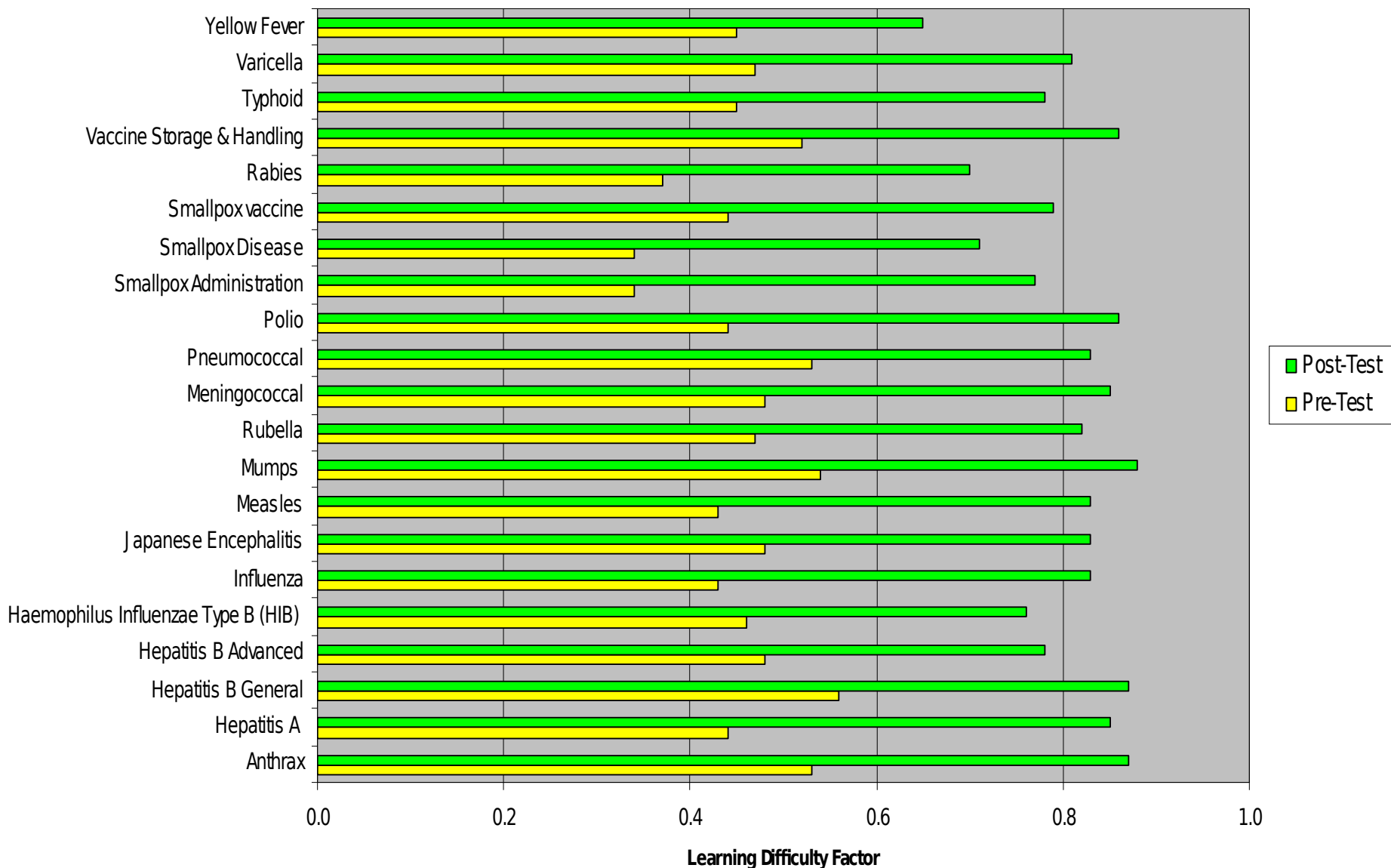


# Education of Healthcare Workers Providing Immunization Services

- Web-based, interactive Learning Management System (LMS)
  - Designed for medical technicians, nurses and clinical providers
  - Curriculum consensus committee identified 21 vaccine and vaccine-related topics for course modules
  - Web-based education development company, was contracted to develop story boards supporting modules development.
  - Modules peer-reviewed & approved by Department of Defense (DoD) multidisciplinary vaccine experts
- Self-paced, objective-testing education modules accessed via **[www.vhcinfo.org](http://www.vhcinfo.org)** (PIR) for CME or CEU credit
  - Users completed pre-test, interactive module, & post-test in sequence
  - Learning gain indices were calculated based on average mean pre-test/post-test scores.
  - Data collected with no personal identifiers as part of a quality assurance process attempting to address module effectiveness to produce learning gains in the user



# Project Immune Readiness (PIR) Pre & Post-Test Learning Difficulty Factor





# **Blistering Skin Rash or Oral Ulcers Post Anthrax Vaccine**

- Three cases identified with history of new onset pemphigus vulgaris post vaccination
  - Positive autoantibodies to desmoglein skin antigen 3 (DSG-3) not present pre-vaccination but appearing after vaccination
- VAERS reports of oral ulcers or blistering skin rashes in temporal association with anthrax vaccine: X out of Y total
- Protocol to assess frequency of new onset anti-DSG3 or -DSG1 post anthrax vaccine
  - Fully approved mid-March 2004



# VHC Network Updates

VAERS update as of 4 May 2004: ANT > 1.1 million immunized, > 4.2 million doses

- 34 VAERS with anthrax vaccine & rash vesicular bullous
  - 19 anthrax alone, others anthrax plus other vaccines
  - COSTAR search terms: rash vesic bull search
  - 4 hospitalized
- Age distribution or reports
  - 18-29 years 20
  - 30-39 years 11
  - 40-49 years 3
- Onset of symptoms: 29/34 within 30 days
- Additional reports with oral ulcers 6
  - 4 with prolonged symptoms "not recovered"



# **Desmoglein Skin Antigens Specific Antibodies Post Anthrax Vaccine**

- **Hypotheses**

- Pemphigus vulgaris specific antibodies against skin antigens may develop following immunization with the anthrax vaccine in a subpopulation of the vaccinated individuals.
- Populations who have received both smallpox and anthrax vaccination will develop auto-antibodies to skin antigens at higher titers and greater frequency than those seen with anthrax vaccination alone.
- Service members with new onset Pemphigus vulgaris will have evidence of anthrax vaccination within 3 months prior to the first presentation of disease and/or evidence of specific antibody to protective antigen (PA), which reflects anthrax vaccine exposure.



# Objectives for Study

- Prevalence of measurable anti-DSG antibodies
  - Baseline, pre anthrax versus post anthrax vaccination
  - Baseline, pre versus post anthrax + smallpox vaccination
- Prevalence of measurable anti-DSG and anti-PA antibodies (as measure of anthrax vaccine exposure) in patients with Pemphigus vulgaris identified in DMSS
  - Currently 11 out of 42 received anthrax vaccine repeatedly after diagnosis
  - Determine if vaccine boosted pathogenic autoantibodies
- Implications of data:
  - Consideration of clinical guidelines that would make Pemphigus vulgaris and blistering oral ulcers and/or blistering skin rashes a relative contraindication to continued anthrax vaccination
  - Further studies on sub-clinical forms of this adverse event?



# **Pemphigus Specific Autoantibodies Protocol Design**

- Systems to be accessed
  - DoD Serum Repository
  - Immunization Registry
  - Defense Medical Surveillance System
- Study Groups: sera for anti-DSG & anti-PA Ab
  - 1: 300 subjects who received at least 3 doses of anthrax vaccine and no smallpox vaccine
    - Sera within 1 year prior to 1<sup>st</sup> dose and sera 21-42 days post 3<sup>rd</sup> dose
  - 2: 300 subjects similar to Group 1 but with smallpox vaccine within 72 hours of 1<sup>st</sup> dose of anthrax
  - 3: All sera from patients with Pemphigus vulgaris (about 11 had anthrax vaccine at some time in course)

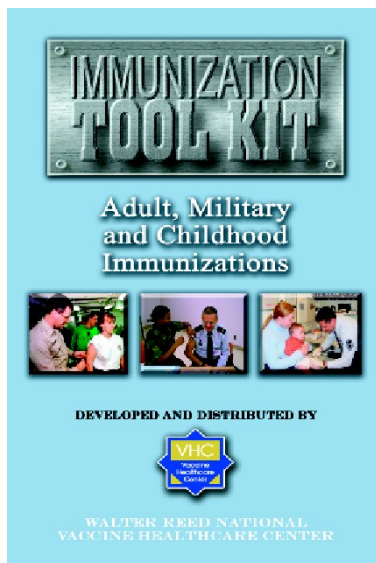


# **VHC Network AFEB Support Requested**

- Recommendation that all patients with post vaccinia cardiac disease be referred to WRAMC or BAMC for standardized evaluation and follow up
  - Difficulties encountered at other sites with obtaining needed studies such as MRI with gadolinium, Indium scan, etc.
- Recommendation that myopericarditis registry for follow up VAERS be extended to 2 years or longer if still symptomatic – objectify QOL impact
  - Consider questions of evolution or recurrence
- Recommend registry for blistering skin disease and/or oral ulcers following vaccination with serum repository to assess anti-DSG autoantibodies



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# **Pemphigus Vulgaris**

## **VHC Network Collaboration**

- 2003 partnership with Dr. Stanley from U of Pennsylvania: immuno-dermatologist with PV expertise, auto-antibody assays
  - Serial serum examinations performed under existing NIH grant for PV: pattern temporally associated
  - Protocol developed to study pre & post anthrax vaccination sera: determine incidence of new onset anti-DSG AB's in vaccinated/unvaccinated group
    - Approved Dec 2003 – accessing DoD Serum Repository
    - Funding for assays under Dr. Stanley's NIH grant expansion
    - VHC Network able to collaborate and leverage research \$
- Biologic plausibility of causal relationship
  - Molecular mimicry as a potential mechanism?



## Project Immune Readiness (PIR) Vaccine Module Pre & Post-Test Learning Gain Indices

